REMARKS/ARGUMENTS

The amendments set forth above and the following remarks are responsive to the points raised by the Office Action dated July 17, 2008, and discussed during the telephone interview with Examiner Li on December 4, 2008. In view of the amendments set forth above and the following remarks, reconsideration is respectfully requested.

As an initial point, the Applicants' representative greatly appreciates the courtesy shown him, Stephanie M. Lawley, and Dr. Patrick Hwu by Examiner Li, and further appreciates her careful consideration of the arguments presented during the interview.

The Pending Claims

Claims 41 and 94-111 are pending. Claim 41 is amended to define the invention more clearly. No new matter has been added, and the basis for the amended claim language may be found within the original specification, claims, and drawings.

Claim 41 is supported by, for example, paragraphs [0041], [0042], [0053], [0056], and [0056] of the specification.

Rejection under 35 U.S.C. § 112

Claims 41 and 94-111 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

According to the Office Action, the recitation of "a preselected antigen" in claim 41 is unclear as to the identity of the antigen, how it is related to the antigens on the allogeneic cell, and/or the chimeric receptor, and makes the metes and bounds of the claim uncertain.

Claim 41 is amended to remove the term "preselected antigen," thus obviating the indefiniteness rejection of claim 41.

Rejection under 35 U.S.C. § 103

Claims 41, 94-103, 105, 106, and 108-111 are rejected under 35 U.S.C. § 103 as allegedly obvious over Hwu et al., *Cancer Res.* 55: 3369-3373 (1995) (hereinafter, "Hwu") in view of Munz et al., *J. Immunol.* 162: 25-34 (1999) (hereinafter, "Munz").

Claim 104 is rejected under § 103 as allegedly unpatentable over Hwu in view of Munz as applied to claims 41, 94-103, 105, 106, and 108-111, and further in view of U.S. Patent No. 5,844,075 to Kawakami et al. (hereinafter, "Kawakami").

Claim 107 is rejected under § 103 as allegedly unpatentable over Hwu in view of Munz as applied to claims 41, 94-103, 105, 106, and 108-111, and further in view of U.S. Patent No. 6,410,319 to Raubitschek et al. (hereinafter, "Raubitschek").

Each of these rejections is separately and respectfully traversed.

Claim 41 is directed to a method of preparing dual specificity lymphocytes. Claim 41 is amended to positively recite contacting lymphocytes in a mixed population of cells with a cell that is allogeneic to one or more lymphocytes, in accordance with the Examiner's suggestion. Amended claim 41 further recites that contacting lymphocytes with the allogeneic cell selects and specifically amplifies, from the mixed population of cells, lymphocytes comprising an endogenous receptor that is reactive with the allogeneic cell. Claim 41 further recites transducing the lymphocytes comprising the endogenous receptor reactive with the allogeneic cell with a chimeric receptor gene that encodes a chimeric receptor that is reactive with a tumor antigen to produce dual specificity lymphocytes.

The presently claimed method is not obvious to one of ordinary skill in the art over the cited combination of references because successfully generating a potent immune response against a tumor antigen using dual specificity T cells is difficult, and at best, unpredictable.

The Applicants submit herewith a declaration under 37 CFR §1.132 of Dr. Patrick Hwu,[1] one of the named inventors of the present patent application, and an author of several peer-reviewed journal articles, including Hwu, Kershaw et al. *Nature Biotechnology*, 20:

[1] An unsigned copy of the declaration is submitted in addition to the signed copy for legibility.

1221-27 (2002) (hereinafter, "Kershaw") (copy submitted herewith), and Murphy et al. *Cancer Gene Therapy* 14, 499-508 (2007) (copy submitted herewith) (Hwu declaration, ¶ 1).

As Dr. Hwu explains, successfully generating a potent immune response against a tumor antigen using dual specificity T cells is difficult, and at best, unpredictable (Hwu declaration, ¶ 5). As explained by Dr. Hwu, tumor antigens are generally weak antigens (see, e.g., Kershaw, page 1221, 1st par. and Murphy et al., page 505, 1st full par. left column) (Hwu declaration, ¶ 5). Accordingly, tumor antigens are not potent enough to generate an immune response to a tumor while allogeneic cells are powerful immunogens, but are not capable of generating a specific immune response to a tumor, as Dr. Hwu explains (Hwu declaration, ¶ 5).

In addition, as Dr. Hwu attests, a T-cell that expresses two distinct receptors can exhibit "cross-antagonism," in which the binding of a ligand to one receptor can inhibit a response to the second receptor (Hwu declaration, ¶ 6). One study, for example, used cell lines that expressed two receptors with different specificities and evaluated whether engagement of one receptor by a peptide would result in inhibition of the activation of the T cell line when stimulated by another peptide (Yang et al., *J. Immunol.,* 170: 4532-38 (2003), copy submitted herewith) (hereinafter, "Yang"). Yang showed that an antagonist for one receptor inhibited cell proliferation in response to stimulation of the other receptor (cross-antagonism) in both class I and class II-restricted, dual-specificity T cells (Yang, page 4536, right column, last par.) (Hwu declaration, ¶ 6). Therefore, the success of the dual specificity T cells produced by the claimed method in generating a potent immune response against a tumor antigen would not be predictable.

Another difficulty in generating a potent immune response against a tumor antigen using dual specificity T cells, as Dr. Hwu explains, is that because the potency of the alloreactive response is so strong, the alloreactive response commandeers the internal "machinery" of the cell (such as, e.g., ZAP 70, and kinases for signal transduction) (Hwu declaration, ¶ 7). Therefore, it would not be expected that the introduction into and expression of an exogenous chimeric receptor in the alloreactive cell to produce "dual specificity lymphocytes" would be successful (Hwu declaration, ¶ 7).

In further illustration of the difficulty in generating a potent immune response against a tumor antigen using dual specificity T cells, as described in Example 1 of the patent application, the T-cells generated by a method similar to that described in Hwu failed to effectively treat cancer. As explained by Dr. Hwu, eight patients with advanced ovarian cancer were treated with T-cells transduced in a method similar to that described in Hwu with a chimeric receptor gene (MOv-γ) (Hwu declaration, ¶ 8). The cells did not specifically localize at tumor sites (Hwu declaration, ¶ 8). As Dr. Hwu further explains, despite specific *in vitro* reactivity of MOv-PBL against ovarian cancer cells, none of the patients responded to the lymphocyte infusion (Hwu declaration, ¶ 8). As Dr. Hwu further attests, the majority of transduced cells were undetectable in circulation between 12-31 days following MOv-PBL infusion (see also, the patent application, Example 1 and Figure 2) (Hwu declaration, ¶ 8).

In contrast to the difficulty and unpredictability of generating a potent immune response against a tumor antigen using dual specificity T cells and in contrast to the poor clinical results achieved as described above, T-cells generated in accordance with the claimed method provided superior experimental results in mice. Specifically, the claimed method provides dual specificity T-cells specific for both 1) a tumor antigen and 2) an allogeneic cell so that during treatment of a patient, the reactivity of the T-cells against the tumor antigen can be bolstered with immunization with allogeneic cells, as explained by Dr. Hwu (Hwu declaration, ¶ 9).

As explained by Dr. Hwu and as described in Example 5 of the present application, mice received dual specificity T-cells "comprising the endogenous receptor reactive with the allogeneic cell" that were transduced with "a chimeric receptor which is reactive with a tumor antigen" (MOv-γ) followed by subcutaneous immunization with allogeneic splenocytes (Hwu declaration, ¶ 10). Mice were later challenged with ovarian cancer tumor cells. As shown in Figure 5 of the patent application, *in vivo* immunization with allogeneic splenocytes from donor mice, combined with administration of dual specificity T cells "comprising the endogenous receptor reactive with the allogeneic cell" that were transduced with "a chimeric receptor which is reactive with a tumor antigen" (MOv-γ), protected mice much more significantly than T cells alone. As explained by Dr. Hwu, the combined conditions result in 100% tumor-free mice while mice infused with dual specificity T cells alone resulted in 25%

tumor-free mice (Hwu declaration, ¶ 10). These results were also published in Kershaw (see page 1223, left column, Figure 5A).

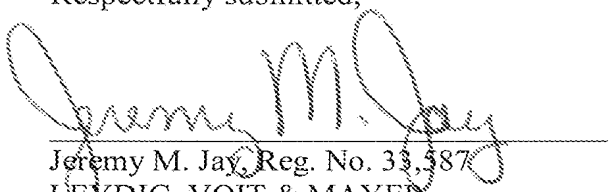
As further explained by Dr. Hwu, Example 6 of the present application further illustrates that dual specificity T cells that were produced according to the claimed method provided superior experimental results in mice, in contrast to the poor clinical results described above. In Example 6, mice were injected with tumor cells. Three days later, the mice received either dual specificity T-cells "comprising the endogenous receptor reactive with the allogeneic cell" that were transduced with "a chimeric receptor which is reactive with a tumor antigen" (MOv-γ), non-dual specific T cells, or no treatment. Mice were immunized with allogeneic splenocytes on days 5, 8, and 11. The dual specificity T cells inhibited the tumor and this effect was augmented by immunization. As explained by Dr. Hwu and as shown in Figure 6 of the patent application, mice that were injected with dual specificity T-cells "comprising the endogenous receptor reactive with the allogeneic cell" that were transduced with "a chimeric receptor which is reactive with a tumor antigen" and immunization or boost, resulted in the smallest tumor size throughout the time course of 29 days (Hwu declaration, ¶ 12). These results were also published in Kershaw (see page 1223, left column, Figure 5B).

Because the presently claimed methods produce T-cells that provide superior experimental results in mice in contrast to the unpredictability and difficulty of generating a potent immune response against a tumor antigen using dual specificity cells and in contrast to the poor clinical results described above, the presently claimed methods cannot be considered obvious over the cited references to one of ordinary skill in the art.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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